

Placental mesenchymal stromal cells rescue ambulation in ovine myelomeningocele.

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Public Summary:

Myelomeningocele (MMC)-commonly known as spina bifida-is a congenital birth defect that causes lifelong paralysis, incontinence, musculoskeletal deformities, and severe cognitive disabilities. The recent landmark Management of Myelomeningocele Study (MOMS) demonstrated for the first time in humans that in utero surgical repair of the MMC defect improves lower limb motor function, suggesting a capacity for improved neurologic outcomes in this disorder. However, functional recovery was incomplete, and 58% of the treated children were unable to walk independently at 30 months of age. In the present study, we demonstrate that using early gestation human placenta-derived mesenchymal stromal cells (PMSCs) to augment in utero repair of MMC results in significant and consistent improvement in neurologic function at birth in the rigorous fetal ovine model of MMC. In vitro, human PMSCs express characteristic MSC markers and trilineage differentiation potential. Protein array assays and enzyme-linked immunosorbent assay show that PMSCs secrete a variety of immunomodulatory and angiogenic cytokines. Compared with adult bone marrow MSCs, PMSCs secrete significantly higher levels of brain-derived neurotrophic factor and hepatocyte growth factor, both of which have known neuroprotective capabilities. In vivo, functional and histopathologic analysis demonstrated that human PMSCs mediate a significant, clinically relevant improvement in motor function in MMC lambs and increase the preservation of large neurons within the spinal cord. These preclinical results in the well-established fetal ovine model of MMC provide promising early support for translating in utero stem cell therapy for MMC into clinical application for patients.

Scientific Abstract:

Myelomeningocele (MMC)-commonly known as spina bifida-is a congenital birth defect that causes lifelong paralysis, incontinence, musculoskeletal deformities, and severe cognitive disabilities. The recent landmark Management of Myelomeningocele Study (MOMS) demonstrated for the first time in humans that in utero surgical repair of the MMC defect improves lower limb motor function, suggesting a capacity for improved neurologic outcomes in this disorder. However, functional recovery was incomplete, and 58% of the treated children were unable to walk independently at 30 months of age. In the present study, we demonstrate that using early gestation human placenta-derived mesenchymal stromal cells (PMSCs) to augment in utero repair of MMC results in significant and consistent improvement in neurologic function at birth in the rigorous fetal ovine model of MMC. In vitro, human PMSCs express characteristic MSC markers and trilineage differentiation potential. Protein array assays and enzyme-linked immunosorbent assay show that PMSCs secrete a variety of immunomodulatory and angiogenic cytokines. Compared with adult bone marrow MSCs, PMSCs secrete significantly higher levels of brain-derived neurotrophic factor and hepatocyte growth factor, both of which have known neuroprotective capabilities. In vivo, functional and histopathologic analysis demonstrated that human PMSCs mediate a significant, clinically relevant improvement in motor function in MMC lambs and increase the preservation of large neurons within the spinal cord. These preclinical results in the well-established fetal ovine model of MMC provide promising early support for translating in utero stem cell therapy for MMC into clinical application for patients. **SIGNIFICANCE:** This study presents placenta-derived mesenchymal stromal cell (PMSC) treatment as a potential therapy for myelomeningocele (MMC). Application of PMSCs can augment current in utero surgical repair in the well-established and rigorously applied fetal lamb model of MMC. Treatment with human PMSCs significantly and dramatically improved neurologic function and preserved spinal cord neuron density in experimental animals. Sixty-seven percent of the PMSC-treated lambs were able to ambulate independently, with two exhibiting no motor deficits whatsoever. In contrast, none of the lambs treated with the vehicle alone were capable of ambulation. The locomotor rescue demonstrated in PMSC-treated lambs indicates great promise for future clinical trials to improve paralysis in children afflicted with MMC.

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